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CLINICAL AND SEROLOGICAL CHARACTERISTICS OF THE EARLY SYSTEMIC LUPUS ERITHEMATOSUS

321.04 - Rheumatology

Summary of doctoral thesis in medical sciences

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The thesis was elaborated in the Department of Internal Medicine, Internal medicine-semiology discipline, Cardiology discipline, at the clinical base of IMSP Institute of Cardiology, State University of Medicine and Pharmacy "Nicolae Testemitanu".

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Introduction. Recognition of early systemic lupus erythematosus (SLE) features is a priority issue in the evolution of the disease. Highlighting the symptoms at the onset of the disease, such as the dynamics and succession of their onset, is fundamental for early diagnosis and favourable prognosis. The international data presented the signs and symptoms characteristic for the early period of SLE, namely the first 2 years after the diagnosis, but in small studies with contradictory results, especially in countries of South America. It should be noted that in analysed literature, we established that the immunological criteria could be detected in patients 5 years before the diagnosis. Based on the results of available studies, we did not identify the symptomatology stage according to the consecutive appearance of it in the early phase of the disease until the diagnosis and in the first years of the disease.

Data in the field of the problem's research. The results of the recent investigations in the field suggest varied incidence and prevalence of the SLE. The highest data were estimated in North America at 23,2 / 100,000 person-years and 241/100 000 persons, respectively, while the lowest incidence data were reported in Africa and Ukraine (0,3 / 100,000 person-years), and the lowest prevalence was in North Australia (0 cases in a sample of 847 persons) [5]. The incidence ratio of women-men varies with age and represents, according to the latest data 7-15: 1 in adults and 3-5: 1 in children [1]. Improving the diagnostic criteria for the disease over the last decades by revising the ACR criteria in 1997 and introducing the 2012 SLICC criteria has resulted in a more efficient identification of lupus patients [8]. At the same time, the vector of the researches of the last years has been directed to clinical and immunological manifestations at onset of SLE, but also in the first years of the disease in order to improve the classification criteria of the disease, with increasing their sensitivity, but also their specificity, in order to shorten the time of diagnosis. Thus, the time of establishing the diagnosis has been shortened in the last decades from 50 months, for the 2000s, to 12 - 20 months for the last decade [3,6]. The shortest period declared in the literature during the last years in an Italian cohort was 9 months [2]. There is a tendency in the researches of the last years to appreciate the characteristics of the early disease and the manifestations of lupus onset, with the purpose of an early diagnosis, and later to choose the treatment tactics needed at the current stage of the disease and its correct management. The above-mentioned data served as a reference for the initiation of a complex research of the early disease in patients with SLE. On this base, we aimed to conduct a descriptive study, which would allow customizing the initial clinical and immunological manifestations in the patients with SLE in the Republic of Moldova to improve and reduce the time of the disease diagnosis and intervention through optimal treatments in order to approve the prognosis in these patients.

The aim of the research was to evaluate the clinical and immunological manifestations of early lupus in relation to late lupus for the elaboration of optimal patient management.

To achieve the goal were outlined the following **objectives**:

1. Estimation of the symptoms that preceded SLE
2. Highlighting the consecutive appearance of clinical signs in early SLE
3. Assessment of the activity of the disease, the organ damage and the quality of life in the patients with early SLE vs late SLE
4. Determining the degree of adherence to the treatment and the predicting factors that diminish it
5. Elaboration of the scheme of management of patients with early SLE

The novelty and the scientific originality: In this study, for the first time, the early clinical signs of SLE and the succession of their occurrence were evaluated, in order to detect their relevance for approving the diagnosis and preventing the irreversible organic damage. The patients' attitude towards the indicated medication according to the self-administered questionnaire MMAS-8, as well as the quality of life in the patients with early and late SLE were analysed.

The scientific problem solved in the thesis. The need to identify the spectrum of early manifestations of SLE, as well as the utility of assessing the characteristics of early disease through modern clinical instruments for proper management in the evolution of the disease, has been made.

Theoretical significance of the work. The research described the types of clinical and serological manifestations in patients with early SLE in correlation with their occurrence, disease activity and organic lesions according to SLAM, SLICC / ACR versus LES after 2 years.

The applicative value of the work. The results of the study argued the implementation in practice of patient management scheme for the early diagnosis of SLE, which will lead to the prompt initiation of treatment, to prevent exacerbations, to improve the prognosis of the disease and to maintain the capacity to work. Consistently, we have supported the informativity and usefulness of the clinical instruments for the evaluation of the disease in its early stage.

Main scientific results submitted for support:

~Determining the clinical and immunological manifestations that preceded SLE diagnosis

~Assessment of the consecutive appearance of clinical and paraclinical signs in early SLE

~Reasoning the usefulness of the clinical instruments for evaluation of the disease activity, organ damage and the quality of life in the patients with early versus late SLE

~Argumenting the usefulness of the degree of adherence to treatment and estimating the predictive factors that diminish it

~Developing a prototype for the patients' management in early SLE

Implementation of scientific results. The results of the study were used in the teaching process of the Department of Internal Medicine and were used in the elaboration of the National Clinical Protocol "Systemic lupus erythematosus in adults" and the sessions of "School of the patient with lupus".

Approval of scientific results. The results of the research were reported at 17 national and international forums: International Congresses: The 9th European Lupus Meeting, Athens, 2014; "MedEspera", Chisinau, 2016; EULAR, Madrid, 2016; Balkan Medical Week, Bucharest, 2016; Balkan Medical Week, Sofia, 2017; LUPUS & ACA 2017, Melbourne, 2017; EULAR, London, 2017; The IMS Congress of Bucharest, Bucharest, 2017; "MedEspera", Chisinau, 2018; Balkan Medical Week, Athens, 2018; ERS International Congress, Paris, 2018; PANLAR, 2018; EULAR, Amsterdam, 2018; EULAR, Madrid, 2019; national forums: University Days and the Annual Scientific Conference of USMF Collaborators and Students "Nicolae Testemitanu", Chisinau, 2017, 2018, 2019.

Thesis based publications. The study materials were reflected in 35 publications, including 8 articles in reviewed journals, 2 monoauthor publications, 5 clinical cases in scientific collections, cassettes from the national clinical protocol on SLE in adults; 18 participations in national and international scientific forums through summary presentations and communications. **Keywords:** early systemic lupus erythematosus, quality of life, comorbidities, adherence to treatment. Summary of the

thesis. The thesis is presented on 118 pages of electronic text consisting of introduction, 4 chapters, 2 clinical cases, conclusions and recommendations, bibliographic indices (126 titles). The paper is illustrated with 25 figures, 16 tables and 10 annexes. The conduct of the study obtained the favourable opinion of the Research Ethics Committee (No. 66 of 16.06.2016) of the PI SUMPh "Nicolae Testemitanu". The researched subjects signed the voluntary informed consent prior to participating in the study.

THE CONTENT OF THE THESIS

INTRODUCTION

The Introduction section addresses the theoretical aspects of the components analysed in the research, the actuality of the topic, the purpose and objectives of the study, the novelty and the scientific originality of the obtained results, the theoretical and applicative significance of the paper, the approval of the results and the summary of the thesis.

1. THE CLINICAL-EVOLUTIVE PARTICULARITIES OF THE PREVIOUS SYSTEMIC ERITEMATOS LUPUS (Literature Review)

Chapter 1 is a summary of the data from the specialized literature regarding the early manifestations of systemic lupus erythematosus and the characteristics of the disease at this stage. We related the contemporary information regarding the epidemiology and the ethiopathogenetic hypotheses in lupus, the development of the diagnostic criteria used in the rheumatological practice. We marked the subject of the clinical manifestations preceding the disease at the time of diagnosis as well as the time required for its establishment by comparing the data from the displayed literature.

2. MATERIALS AND METHODS OF RESEARCH

2.1. The clinical-statutory characteristics of the study group

In accordance with the purpose of the transversal study and the investigative objectives set, a batch of 202 patients was diagnosed with SLE diagnosis, established according to the classification criteria SLICC, 2012.

Inclusion criteria:

1. The systemic erythematous lupus, confirmed by the presence of 4 or more criteria of classification SLICC, 2012
2. Age over 18 years
3. Obtaining informed consent from the patient
4. The medical insured patient

Exclusion criteria:

1. The patient's refusal
2. Other autoimmune diseases.

Thus, the final research group consisted of 202 patients with SLE, evaluated multidimensional. The characteristic of the demographic parameters of the disease in the patients in the study group indicates that the age of the patients at the onset of the disease was included in the wide variational intervals: 13 and 67 years with the average age of 34,52 years, the duration of the disease has varied from the recent onset. – 0,5 months to the long duration of the disease - 432 months. It should be noted that the average time for diagnosis in the study patients was 9,31 months, and ranged from 1 month to 48 months.

2.2. Methods for clinical and paraclinical examination of patients

The patients included in the research were examined according to the design of the study by general and special methods according to the questionnaire elaborated by us. Further evaluation of the patients included in the research involved their self-division into two groups, according to the duration of the disease. The plan of the examinations of the patients from the framing in the study and subsequently, after the division into batches is carried out in figure 1.

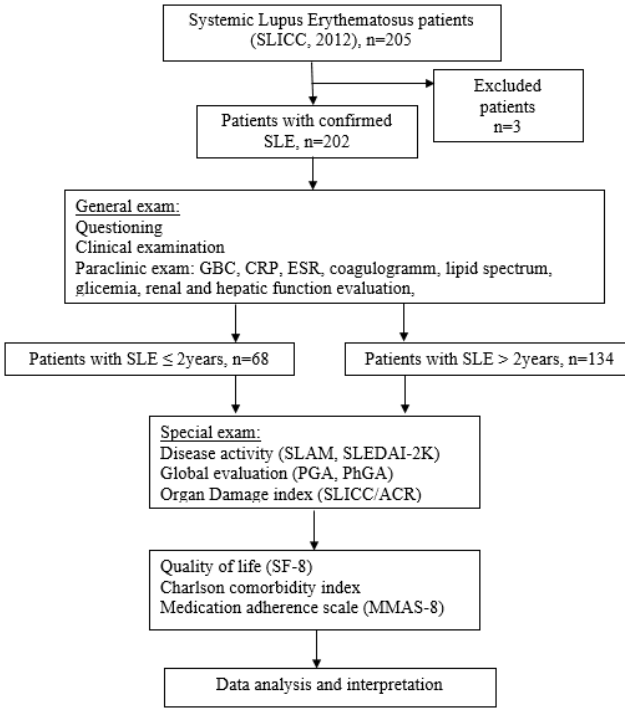

Figure 1. **Study design.**

According to the Treat-to-Target (T2T) recommendations for the correct management of patients, it is necessary to evaluate based on disease activity, irreversible organ damage, quality of life of patients and comorbidities of the disease. In order to evaluate these parameters, validated clinical instruments have been used, which have demonstrated their effectiveness and specificity. The activity of the disease was assessed according to the specific clinical instruments: SLEDAI-2K (SLE Disease Activity Index 2000) - the gold standard in international clinical practice and the Systemic Lupus Activity Measure (SLAM) predominantly used in clinical studies. The global assessment of the disease was evaluated by the Physician Global Assessment (PhGA) and the Patient Global Assessment (PGA) through the VAS (0-100mm). Organ Damage Index (SLICC / ACR DI), the tool developed by the SLICC / ACR group to assess irreversible organic damage and includes the evaluation of 12 organ systems determined in at least 6 months of disease. The estimation of the comorbidities in the patients in the study was performed using the Charlson Index, the age-adjusted variant, which represents a score for the evaluation of the concomitant pathologies, determining their impact by calculating the survival risk adjusted over the next 10 years. Quality of life was assessed through the self-administered survey Short Form-8 (SF-8), the short version of the most used SF-36 survey. SF-8 is an 8-item tool that appreciates the general aspect of health related quality of life. We found it appropriate to further assess the adherence to treatment indicated in the study patients by using the Morisky Medication Adherence Scale (MMAS-8), considered the most commonly used self-report method for determining treatment adherence.

2.3. Methods of statistical analysis of accumulated data

The accumulated data were processed computerized by performing a variational and correlational calculation using the statistical programs MedCalc statistical software (version 12.7.0.0.) and Microsoft Excel. The structure and dynamics of the investigated phenomena were examined using the statistical methods with the appreciation of the arithmetic means (M), the standard deviations (SD) and the confidence interval (CI). The degree of correlative association between the evaluated parameters was estimated by applying the correlation coefficient r (Pearson). The conclusion of the differences between the average values of the studied parameters was estimated using the t-Student criterion. The graphical representation of the distribution of the maximum and minimum values, the arithmetic mean and the standard deviation was possible through the Box-Plot analysis.

3. SPECTRUM OF MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS IN PATIENTS IN THE STUDY COHORT

3.1. Clinical-statutory characteristic of the research group

As a result of the descriptive cross-sectional study, the sample was self-divided into two groups: duration of disease up to 2 years, called early lupus, which included subjects whose diagnosis was established in the last 24 months, and late or constituted lupus, which included subjects with disease duration more than 2 years. We started the analysis of the study groups by comparing its demographic aspect. Thus, we reported the predominance of women in both groups and the rural residence, 52,94% and 50,75%, respectively among patients in study group I and II. Regarding the matrimonial status, we found the predominance of married persons, which constituted 52,94% and 65,67% respectively. At the same time, in the group of patients with early and late lupus divorced persons, widows or singles were 47,06% and 34,33% respectively. We continued by evaluating the age at the time of the research, which was included in wide variation intervals, from 18 to 73 years, with the average of age in Lot I 39,60 years versus 45,50 years in Lot II. At the same time, the age at onset for both groups was within a wide range of 20-67 years and 13-60 years, respectively. Regarding the duration of the disease, in the first batch was significantly lower (average – 1,.42 months) compared to group II (average – 146,41 months). Taking into account the difficulty of differentiating the early signs, we accurately estimated the time from the first symptoms to the diagnosis of SLE and found that it was similar in groups: 1-47 months in early lupus and 1-48 months in late lupus group.

Subsequently, we estimated the time from the appearance of the first symptoms attributed to lupus to the confirmation of the diagnosis based on the classification criteria SLICC, 2012. From the data obtained, we concluded that in patients with early lupus the diagnosis was established in shorter terms – 7,08 months compared to 10,74 months in patients from the group of patients with longer disease duration. Next, we segregated the time from the onset of the first symptoms to the address to the healthcare and then till the diagnosis of SLE. In fact, patients referred to the doctor on average in 4,81 months for consultation regarding one or more manifestations that may be conferred SLE. The prompt address was in the case of fever, oedema and serositis. The delay of addressability was established in the case of onset with joint pain, malar rash and photosensitivity. After addressing the doctor the diagnosis of the disease was established on average in 2,27 months, being prolonged on the basis of the necessary paraclinical and immunological tests. Moreover, we can see that the diagnosis period of the disease in the last years has improved due to the high addressability of the patients in the

first 3 months after the manifestation of the disease, but also due to the improvement of the paraclinical explorations in rheumatology.

3.2. Expression of manifestations of early systemic lupus erythematosus

According to the outlined tasks, we intended to identify the early signs of the disease that deserve special attention in the early diagnosis of the disease. Therefore, the clinical picture, from the onset of the disease to the addressing to the healthcare, according to the classification criteria, was determined by the joint involvement in 64,70% cases, the cutaneous involvement manifested by photosensitivity and malar rash in 58,82% and, respectively, 32,35% cases, followed by oral and / or nasal ulcers and diffuse non-scarring alopecia in 26,47% cases. Signs such as maculopapular and discoid rash were rare skin manifestations in the early period, which were found in 5,88% and 2,94% patients. We identified such signs at onset such as pleurisy and pericarditis (8,82% and 2,94% respectively), renal impairment (5,88%), nervous system involvement represented by polyneuropathy (5,88%), as well as haemolytic anemia (1,47%).

With particular attention, we analysed and identified the signs that can be attributed to SLE at the initial stages of the disease excluded from the SLICC classification criteria, 2012. A series of constitutional manifestations such as fatigue in 42,64% patients, fever and weight loss were noted in 29,41% and 14,70% respectively. It should be mentioned that the joint pain without synovitis or morning stiffness was reported by a lot of patients, thus constituting 80,88% cases, myalgia, was detected in 20,58% patients. Regarding lymphadenopathy in the absence of the infectious or malignant process, it was registered in 13,23% cases. Among neurological manifestations omitted from the criteria the important ones proved to be depression and headache in 14,70% and 11,76% subjects, respectively. Involvement of peripheral vessels at onset, manifested by Raynaud's Syndrome and / or livedo reticularis, was found in 20,58% and 14,70% of patients, respectively, as venous thrombosis was less frequently determined - in 2,94% cases. Sjogren's syndrome was present in 11,76% of patients. An important manifestation at the onset of the disease for young patients is spontaneous abortion, which in our study group occurred in 3 patients out of 65 (4,62%).

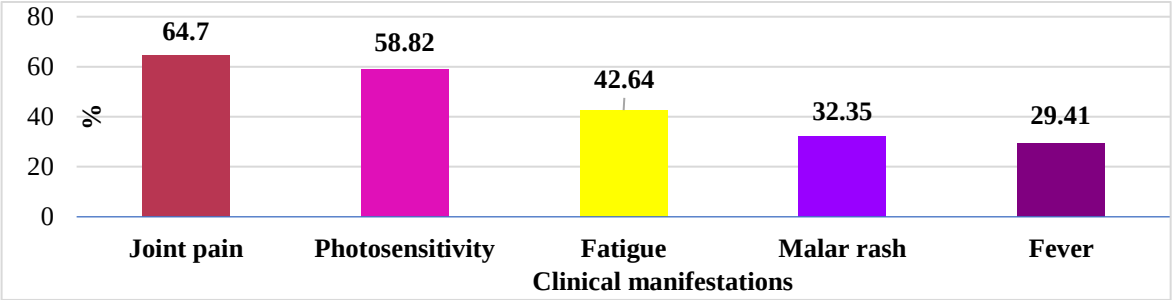

Figure 2. **Top early manifestations of SLE.**

Further, we were motivated to segregate the top of the most frequent manifestations of systemic lupus erythematosus. Moreover, the top three early manifestations in the patients from the study were joint pain, photosensitivity and fatigue, supplemented by cutaneous signs and fever. Subsequently, we directed the research vector to the clinical signs prior to the diagnosis of SLE and stratified them chronologically. The earliest clinical manifestations that can be attributed to lupus were recorded 5 years before the diagnosis of the disease. In this regard, the signs preceding the diagnosis with 5 and 4 years were transient arthralgia, seasonal photosensitivity and episodic fever, at the same time, 2-3 years before, malar rash, weight loss and leukopenia, were found in the medical documents. The year

before the diagnosis was characterized by supplementing the clinical picture with fatigue, fever, thrombocytopenia and proteinuria.

3.3. Clinical picture of lupus in research batches

In the following material we analysed the results of the study from the perspective of 2 groups of investigation - the group with early lupus - 68 patients and late lupus - 134 patients. We initiated the analysis by comparing the disease classification criteria, according to the SLICC 2012 criteria and determined a significant difference between the research groups of the malar rash (p=0,03) and the photosensitivity (p=0,0001) frequency, these manifestations being determined in 44,11% and 61,76% respectively in group I versus 56,71% and 32,84% cases in group II. Other skin manifestations, such as maculopapular rash and chronic lupus, were noted in 8,82% and 5,88% cases in the patients with early lupus and 6,71% and 3,73% cases with late lupus. At the same time, oral and nasal ulcers were determined in about one third of patients with early disease, but more frequently in patients with longer disease duration (41,79%). With regard to alopecia, this was less frequently (p<0,0001) in patients with early disease – 22,06% and 54,47% cases in patients with late lupus.

Joint involvement was found to be more frequent (p<0,0001) in the long-term disease, accounting for 64,70% and 88,05% cases in group I and group II respectively. The frequency of pleural and pericardial effusion in the first years of disease was lower, 14,70% and 8,82% patients with early disease compared to 29,10% and 21,64% respectively in late lupus. Similar data was noted in lupus nephritis and constituted 11,76% and 23,14% patients respectively. The frequency of seizures and psychoses was low in both study groups, while a significantly greater difference of polyneuropathies was determined in patients with a disease duration of more than 2 years (p=0,003).

During the study we evaluated other manifestations characteristic of the disease, which are not included in the classification criteria. Thus, we determined the increased frequency (p<0,0001) of fever in patients with early disease (51,47%) compared with the long disease duration (6,72%). At the same time, weight loss, fatigue and fibromyalgia were noted, but without a significant difference between groups. The analysis of musculoskeletal manifestations determined that myalgia was reported in both groups of patients, and avascular necrosis in the group of patients after 2 years of illness (3,73%). Such skin manifestations as livedo reticularis and Raynaud's syndrome were present in both groups. Ocular disorders were manifested by episcleritis, xerophthalmia, and cataract, more commonly installed in patients with late disease; it should be noted that the frequency of cataract was significantly higher in this group (p=0,05).

The lung involvement was present in the group with late disease, the most frequent being lupus pneumonitis (8,96%). The cardiovascular system was involved in SLE through hypertension, manifested only in patients with late lupus (p=0,001) in 16,42% cases, vascular thrombosis was determined in both study groups. Renal impairment due to acute renal failure was determined only in the group of patients with more than 2 years of disease (1,49%). It should be noted that chronic renal failure was established in 1,47% of patients in group I versus 11,19% in patients in group II (p=0,01). The central nervous system was involved in the lupus process in both groups, manifested by lupus headache and depression, as well as stroke. The gastrointestinal tract was affected by xerostomia, peritoneal serositis and most commonly by gastroduodenal ulcer (p=0,04) in patients with the disease over 2 years. In the study patients there were 15 pregnancies, of which 4,61% in LI and 3,87% in LI

patients had abortions or stagnant pregnancies. Amenorrhea was established only in patients with long-term disease (p=0,005).

Based on the above, we can conclude that in our study the early disease was characterized by the presence not only of the specific signs, which are included in the diagnostic criteria of the disease, but also of the omitted ones, but no less important for establishing the diagnosis. Thus, SLE suspicion is based on the complexity of the disease.

The investigation continued by examining the laboratory criteria for the classification of the disease. Following the research of the haematological parameters, we established leukopenia and lymphopenia in 29,41% and 16,18% patients in LI respectively and in 17,91% cases in group II, and thrombocytopenia was registered in 19,12% and 8,96% cases, respectively. The indispensable criterion for establishing the diagnosis of SLE is the presence of the immunological markers, thus, we appreciated that the antinuclear antibodies had a higher frequency (p=0,04) in the patients with early lupus (92,65%) compared with the late lupus (83,59%). Double-stranded anti-DNA antibodies and low titres of complement fractions C3 and C4 had a higher frequency in the first study group (91,17% and 58,82%) versus group II (88,81% and 49,26%). The presence of antiphospholipid antibodies was characterized by the higher frequency of lupus anticoagulant in group I – 17,64%, followed by anti-CL antibodies and anti-β2GP1 antibodies, only in 5,88% and 2,94%, respectively. The frequency of antiphospholipid antibodies in group II was characterized by the predominance of anti-CL antibodies, as well as the lupus anticoagulant, in 29,85% and 23,88% cases, respectively, with anti-β2GP1 antibodies being determined in 7,46% cases. The anti-Sm antibodies in the patients in the study were significantly (p=0,002) higher in the patients in LI (11,76%) compared to those in LII (5,97%). Carrying out the Coombs test in the clinical absence of autoimmune haemolytic anemia proved the positive test weight in 7,35% patients in group I and only in 2,98% cases in group II.

In conclusion, the set of paraclinical manifestations, including immunological, the most frequent during the early period of the disease was ANA (92,65%), anti-dsDNA (91,17%), low titre of complement fractions (C3, C4) (58,82%), as well as leukopenia (29,41%).

3.4. Evaluation of the disease activity and the organ damage in the patients from the study groups.

The management of SLE is based on T2T recommendations, which are aimed at the early diagnosis orientation, which contributes to the prompt initiation of therapy, to diminish the activity of the disease or to obtain the remission and to approve the prognosis of the disease [4]. For this purpose in the analysing the disease activity in the patients at the time of the research, we used international indices of the disease activity appreciation (SLEDAI-2K and SLAM). The disease activity according to SLEDAI-2K had wider limits in the group of early disease (vi 1-24 p.) compared with the group of patients with late disease (vi 0-18 p.), with a mean score ± SD of 7,85 ± 4,65 and 5,98 ± 4,21, respectively in the study groups, thus determining the significantly higher activity of the disease in group of patients with early disease (p=0,003). The distribution of patients according to the activity level in the research groups was scored by 0 points - remission, 1-5 points - low activity, 6-10 points - moderate activity, 11 points and more - high disease activity.

According to the figure 3, the group of patients with early disease was characterized by the absence of patients in the remission phase compared to the group with the constituted disease (0% vs. 2,24% patients). Patients with low disease activity were smaller in the group of patients with early

disease compared with the longer-term disease (32,36% vs. 44,78%, respectively). The number of patients with moderate disease activity prevailed in patients with early lupus – 44,11% cases compared with 33,58% patients with constituted lupus. Regarding the high activity of the disease, we found the predominance of cases in group I compared with group II, estimated at 23,53% and 19,40% patients respectively.

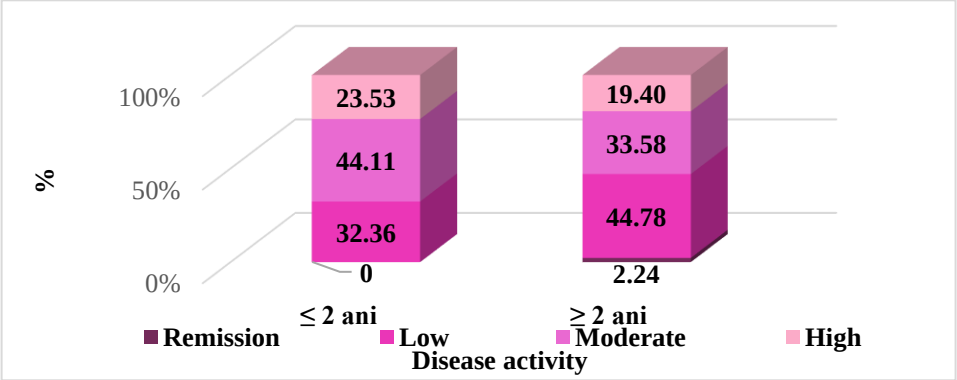

Figure 3. **SLE disease activity according to SLEDAI-2K index in the study groups (%).**

The analysis of the SLAM activity index revealed a mean score ± SD of 7,76 ± 4,64 and 7,34 ± 4,08 in the group of patients with early and late lupus, respectively, without the statistically significant difference between groups p=0,41, when the variation interval varied significantly – 0-26 p. in LI compared to 0-19 p. in LII. In the next stage of our study, we evaluated the activity of the disease at different stages of its evolution and compared the results of the SLAM and SLEDAI-2K indices in the groups of 0-24 months, 25-60, 61-121 and over 121 months (points).

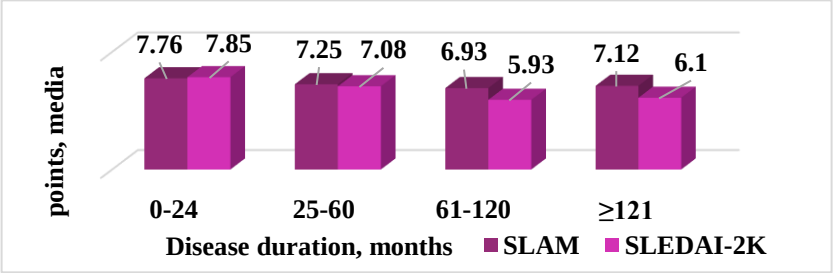

Figure 4. **Disease activity depending on the duration of systemic lupus erythematosus.**

From the figure, we can see that the activity of the disease has a tendency to decrease with time, the highest activity of the disease being in the year 1 and 2 of the disease, according to SLEDAI-2K, whereas the SLAM did not show significant differences. We can explain this difference by analysing the overall SLAM index, which contains objective but also subjective points (headache, cortical dysfunction, fatigue, abdominal pain) in evaluating the activity of the disease, being influenced by the patient's mental well-being at the time of examination.

Further, we evaluated the relationship between the rates of appreciation of the disease activity in two study groups, in order to configure a complex image on the activity of the disease depending on the duration of SLE. Thus we found that PGA and PhGA have a strong statistically significant correlation in both study groups (L1: r=0,735, p<0,0001, L2: r=0,874, p<0,0001). We established the statistically significant relevant relationship between SLAM and SLEDAI in both study groups (L1: r=0,628, p<0,0001, L2: r=0,728, p<0,0001). Comparison of PGA and PhGA indices with disease

activity indices revealed a moderate correlation of SLAM with PGA (L1: r=0,462, p=0,005, L2: r=0,506, p<0,0001). Note that the correlation with PhGA had a moderate significance in L1: r=0,449, p=0,007 and strong in L2: r=0,707, p<0,0001, statistically significant in both groups.

It should be mentioned that SLEDAI in the first study group correlated only with PhGA r=0,352, p=0,04, statistically moderate correlation, and in the group of patients with late disease SLEDAI correlated with both indices. Thus, there was a moderate correlation with PGA (r=0,363, p<0,0001) and a strong correlation with PhGA (r=0,612, p<0,0001), statistically significant in both cases. These data can be explained by underestimation or underassessment of the health status in patients with short-term disease, while over the years living with the disease patients begin to understand and perceive the manifestations of the disease correctly, thus appreciating them more objectively.

Following the above, we can conclude that the early disease was characterised by high activity according to SLEDAI-2K and SLAM, with the subsequent decrease of activity on the treatment background administered in the group of patients with the constituted disease. Patients with a short duration of disease tend to underestimate their overall health status, due to insufficient knowledge in the field and frustrations caused by the onset of the disease. A more objective evaluation of the activity characteristics of the disease was made using the SLEDAI-2K and PhGA indices, which are based on the manifestations and objective signs of the disease at any stage. However, the more complex image of the disease was determined by applying the SLAM and PGA tools, which also contain subjective factors in their evaluation.

4. SETTING UP THE DISEASE MANAGEMENT PILLARS IN DEPENDENCE OF THE DISEASE DURATION.

4.1. Determination of organ damage, comorbidities and disability in lupus patients according to disease duration.

The management of the disease is based on the assessment of the disease activity, the irreversible organ damage, comorbidities and the quality of life, the only instrument of appreciation of the organ damage being the SLICC / ACR DI [7]. In continuation of the idea, we were interested in assessing the irreversible organ damage in the patients from the study groups and we determined that in the group of early patients it constituted on average 0,23 ± 0,43 points, the maximum score being 1 point, rated at 8 (23,52%) patients. In turn, the group of patients with longer duration of the disease was characterized by the more frequent detection of the disease complications, on average 1,08 ± 1,29 points, with a maximum score of 5 points. Thus, the SLICC / ACR IL analysis revealed the occurrence of significantly more irreversible organ damage (p=0,0003) in patients with long duration of the disease. For a clearer understanding of the organ damage depending on the duration of the disease, we analysed the affected organ systems in accordance with the SLICC / ACR DI.

According to the data in figure 5, the early disease was characterised by ocular damage, present in one patient through cataract development. Neurological involvement was characterized by stroke and cognitive impairment, in four patients there were renal changes such as pronounced decrease in glomerular filtration and proteinuria ≥3,5 g/24 hours. Fibrosis of the pleura was detected in one patient, in two cases heart disease was noted by recurrent pericarditis and angina pectoris, and in three cases vascular thrombosis occurred. Regarding the musculoskeletal impairment, we note that in two patients muscular atrophy and joint deformity were determined.

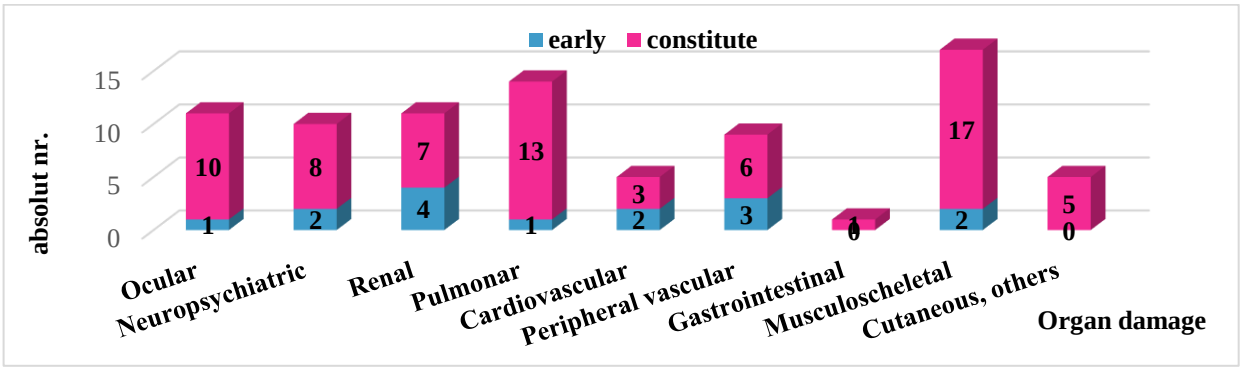

Figure 5. **SLICC / ACR DI impairment pallet in the patients in the study group.**

The group of patients with the constituted disease was characterised by the progression of the organic lesions and the development of the irreversible damage from several organ systems. Thus, cataract was detected in 10 patients. Irreversible neuropsychiatric involvement was manifested by stroke (4 patients), of which one patient with repeated stroke (2 SLICC / ACR points), cognitive disorders (1 patient) and peripheral neuropathies (2 patients). Irreversible renal injury was justified by the presence of diminished glomerular filtration (<40%), proteinuria ≥3,5 g / 24 hours or end-stage renal disease in seven patients. Respiratory system lesions were determined in 13 patients, characterized by pulmonary hypertension in six patients, pulmonary fibrosis - 4 and signs of pulmonary microinfarction in 3 cases. Irreversible lesions of the cardiovascular system were represented by two cases of angina and one case of persistent pericarditis. The incidence of peripheral vascular lesions was influenced by venous thrombosis with swelling or ulceration in six cases. Impairment of the gastrointestinal system was found only in a patient with mesenteric infarction. An increased incidence of irreversible damage from the musculoskeletal system was determined by erosive or deforming arthritis in three cases, complicated osteoporosis with fractures - 9 cases and avascular necrosis in the shoulder or femoral head in 5 cases. Chronic cutaneous lesions were present in 2 patients with chronic scaring alopecia. Other irreversible lesions in the patients in this group were premature gonadal failure, caused by early menopause (up to 40 years), which was found in two cases, and malignancies - malignant formation of the mammary gland in a patient.

Another objective set for the evaluation of the patient, including at the early stage, was the assessment of comorbidities and the comparative analysis of the results obtained after applying the comorbidity assessment tool - the Charlson index. Thus, we obtained a mean ± SD of 1,0 ± 1,39 points (vi 0-5) in the early group and 1,46 ± 1,71 points (vi 0-8) in patients with constituted lupus without statistical significance (p=0,14).

We continued the research by evaluating the types of concomitant diseases at the time of the examination of the patients from both study groups, the results presented in figure 6.

Following the analysis of the data of the concomitant disease's evaluation according to the Charlson index, we established the presence of several pathologies in the patients from both study groups. The most common comorbidities present in patients with early disease were liver disease and peripheral vascular disease, recorded in 5,88% and 4,42% cases respectively. These pathologies were followed by ulcerative disease, chronic obstructive pulmonary disease and diabetes mellitus in 2,94% of cases, concurrently, stroke and chronic kidney disease were determined in 1,47% of patients.

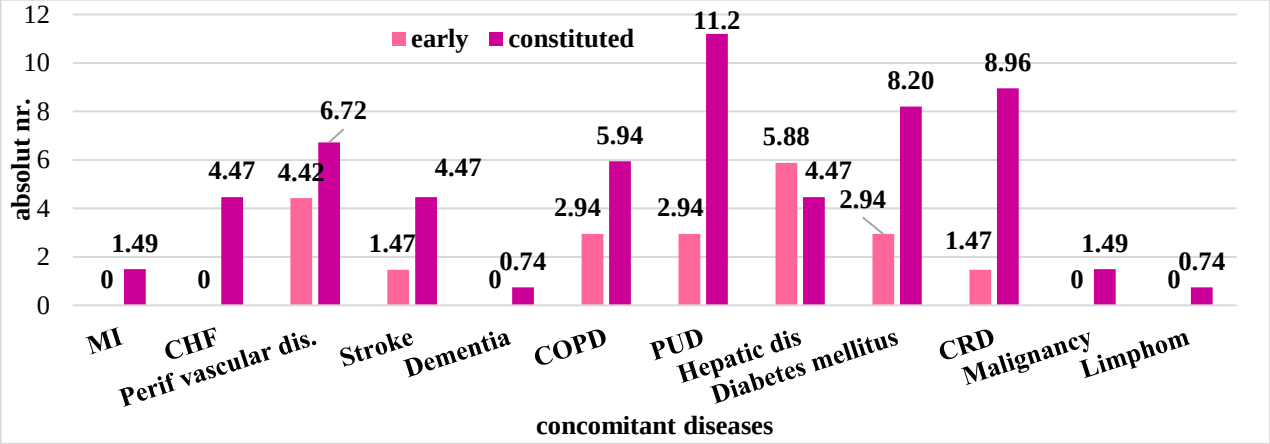

Figure 6. **CCI variables in the study groups.**

Gastric and duodenal ulcers were more frequent in the group of patients with constituted lupus in 11,20% cases, chronic renal disease - in 8,96% cases and type 2 diabetes in 8,20% patients. The concomitant diseases with the lowest frequency were peripheral vascular disease in 6,72% cases, COPD in 5,94% patients. Chronic heart failure, stroke and liver disease were equally found in 4,47% of cases. Such concomitant diseases as myocardial infarction and malignancies were diagnosed in 1,49% of patients. Less frequently, in 0,74% cases, dementia or lymphoma was determined in patients with the disease lasting more than 2 years. Thus, the rest of the pathologies included in the CCI, such as the immunodeficiency syndrome and leukemia, were not detected.

We were tempted to analyse the mutual dependence between disease duration and CCI, suspecting the occurrence of several concomitant pathologies with the increase of the disease duration.

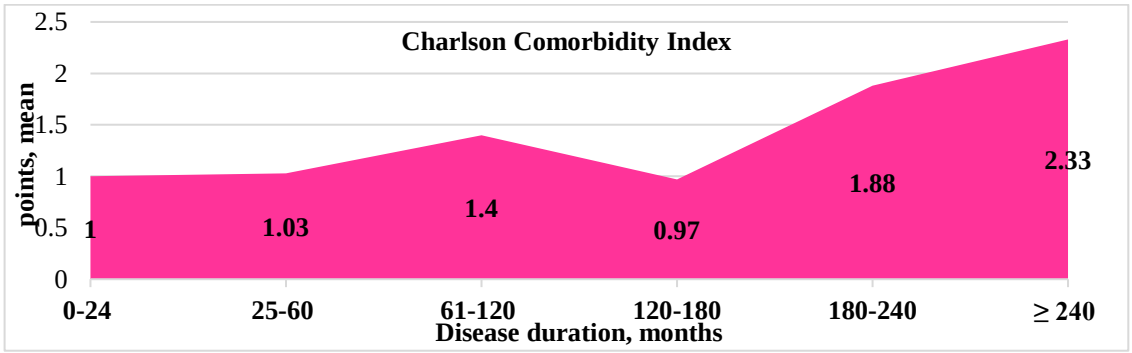

Figure 7. **Charlson index depending on disease duration**

Analysing the data in the figure, we see the tendency of Charlson index to increase with the duration of the disease. Thus, at the early stage of the disease an average of 1 point is noted, which in the following years is increasing and constitutes on average 1,03 points from 2 to 5 years, later 1,4 in the period of 5-10 years. It should be noted, that the period between 10 and 15 years is characterized by a sharp fall in the Charlson index and constitutes 0,97 points. It is obvious that the next period, after 15 years, is distinctive for the significant increase of the Charlson index, possibly due to the age of these patients, but also due to the negative impact of the long-term illness.

We continued the analysis by correlating the activity indices and the organ damage with the Charlson index and highlighting their interdependence in study groups.

The data illustrated in the table 1 show the moderate correlation of the Charlson index with the indexes of patient's and doctor's global assessment, as well as the index of organ damage in both

study groups. It should be noted that the more important statistical significance of these correlations is in the group of patients with the disease lasting more than 2 years, which can be explained by the more accurate understanding and exposure of the overall condition by the patient and subsequently the correct evaluation by the doctor, which reflects on these indices. The organ damage index, in turn, is one of the determinants of comorbid pathologies during the disease, so that with the increase of the disease duration, the organ damage represented by increasing the frequency of the concomitant diseases accumulates.

Table 1. **Correlative analysis of the Charlson comorbidities index in the study groups**

Indexes	CCI LI, n=68	CCI LII, n=134
PGA	r = 0,348, p = 0,043	r = 0,305, p = 0,0003
PhGA	r = 0,445, p = 0,008	r = 0,370, p <0,0001
SLICC/ACR IL	r = 0,354, p = 0,04	r = 0,490, p <0,0001

At the same time, we aimed to analyse the frequency of disability in the patients in the study, considering that lupus is a chronic pathology, which affects the functional capacity of the patients due to various manifestations and complications. Following the research we determined the presence of disability in patients with early lupus only in 23,52% patients. At the same time, an inversely proportional rate of 74,63% was determined among patients with constituted lupus. In further research, we determined the presence of disability in the study patients depending on the duration of the disease, divided into narrower time limits. Thus, a lower rate of disability is observed in the first year of the disease, in only 7,1% of cases, with its subsequent increase in the following years. The cumulative incidence of disability increases after 5 years of illness, being about 80%, with an insignificant difference between the periods of 10, 20 or more years. In conclusion, we can see that the organ damage and the comorbidities are negatively reflected on patients work capacity and productivity, which decreases with the disease duration.

4.2. Assessment of the quality of life of patients with early and installed disease

Morbidity in SLE remains high, with significant potential to affect patient's daily lives, so assessing patients' quality of life is important for the overall determination of the diseases impact, including its early period. Thus, following the analysis of the quality of life in the patients, we registered values lower than the average in both groups, the average being below 50 points, which represents a significant physical and mental suffering in the patients with SLE (figure 8).

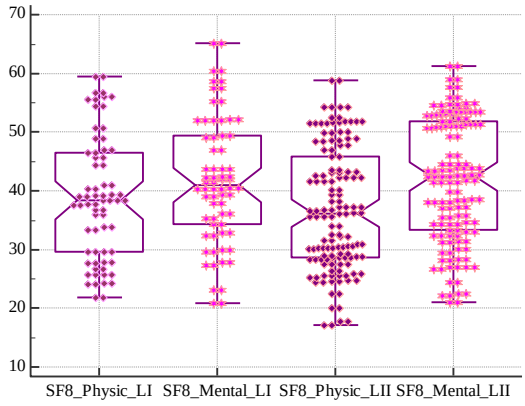

Figure 8. **Boxplot comparative analysis of the quality of life compartments of patients with SLE early and late.**

At the same time, we identified the average values of the physical component, being insignificantly higher in patients with early disease (38,79 ± 10,60) compared with the long-term illness (36,76 ± 10,29) and of the mental component with values similar to patients from both study groups (41,80 ± 10,83 vs. 41,97 ± 10,43, LI and LII, respectively).

In continuation of the idea, we carried out the correlative analysis of the indices of the activity of the disease, the organic injury and the comorbidities on the quality of life of the patients depending on the duration of the disease. Thus, in the group of patients with early disease, we determined a moderate, statistically significant correlation of the mental compartment only with PGA (r=-0,311, p=0,009) and PhGA (r=-0,355, p=0,003), while the physical compartment had a statistically significant, correlation with several indices, such as PGA (r=-0,670, p<0,0001), PhGA (r=-0,581, p=0,0003), SLAM (r=-0,468, p=0,005) and IC Charlson (r=-0,577, p=0,0004). In the group of patients with longer duration of the disease we determined the presence of significant correlation between the mental compartment of QoL and PGA (r=-0,500, p<0,0001), PhGA (r=-0,495, p<0,0001), SLAM (r= -0,291, p=0,0007), DI (r =-0,292, p=0,0006) and comorbidities (r=-0,233, p=0,006). The physical compartment, in turn, was characterized by a mild or moderate statistically significant correlation with all disease parameters: PGA (r=-0,569, p<0,0001), PhGA (r=-0,523, p<0,0001), SLAM (r=-0,380, p<0,0001), SLEDAI (r=-0,326, p=0,0001), DI (r=-0,223, p=0,0095) and comorbidities (r=-0,397, p<0,0001). At the same time, the correlation of the mental and physical compartments in groups revealed the presence of the statistically significant link only in the patients with the longer duration of the disease (LI r=0,154, p=0,3845, LII r=0,246, p=0,004).

4.3. Determining the importance of adherence to treatment in SLE management

The current treatment of SLE is aimed at multiple objectives, which include controlling the activity of the disease, preventing exacerbations and minimizing the complications of the disease or treatment. Therefore, in the further research we analysed the therapeutic regimen when examining the patients included in the study, but also the drugs used in the last year before the selection visit.

Analysis of the therapeutic regimen in the patients in the study groups reveals that all patients (100%) in the early group received GCS at different doses, including pulstherapy, as in the constituted lupus group – 97,01% of the patients. Methylprednisolone at a dose of less than 6 mg per day was significantly less in patients (p=0,0002) with low disease duration versus high disease duration (14,71% vs. 40,29%). The moderate dose (7,5-30 mg / day) was the most commonly used in both study groups (52,94% and 54,47%), while administration of prednisolone doses greater than 30 mg daily noted in patients with early disease (p<0,0001). Another important finding is the administration of GCS in pulstherapy ≥250 mg / day (iv) at least once during the last 12 months, as well as high doses of GCS in the first study group (p<0,0001). The results of the research do not aim at a significant statistical difference in the administration of immunosuppressive treatment with cyclophosphamide, azathioprine, mycophenolate mofetil or methotrexate between groups, however, the difference in hydroxychloroquine therapy was evident in patients with a shorter disease duration (p=0,001). Regarding thromboembolic prevention therapy, we noted similar administration of antiaggregants in groups, while anticoagulant therapy was more frequent in patients with early SLE (p=0,002).

According to the tasks outlined, we analysed patient's adherence to treatment and determined a mean ± SD of 1,88 ± 1,47 points (vi 0-6) in the early group and 250 ± 139 points (vi 0 -6) in patients with constituted lupus, with a significant difference in statistical aspect between groups (p=0,02),

which implies a lower adherence to treatment in patients with longer disease duration compared to patients with early lupus. We were tempted to analyse the number of patients in both study groups according to the fragmentation of the Morisky index in high, moderate and low adherence and we concluded that the predominance of high adherence was characteristic for patients with early disease – 55,88% compared to 31,34% patients with the late disease. The group of patients with the disease older than 2 years was characterized by the predominance of the moderate adherence to treatment in 41,05% versus 36,76% in the early group. Low adherence was determined in only 7,35% of patients with early SLE and 27,61% of patients with constituted SLE. We conclude that patients with SLE have a tendency to decrease the treatment compliance with the probability of neglecting the prescribed complex treatment or the modification of the therapeutic regimen, the indicated doses and the cycles of administration of anticoagulants, indicated by the specialist.

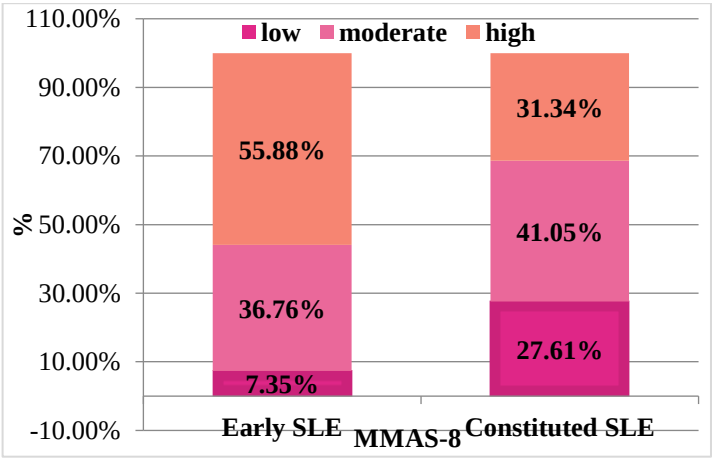

Figure 9. **Treatment adherence in patients with early and constituted lupus.**

The correlative analysis of the Morisky index determined the dependence of treatment compliance on the level of studies of patients with early SLE, with its decrease in patients with a higher level of studies (r=-0,210, p=0,04, LI vs r=0,07, p=0,86, LII). At the same time, the mental state of the patients negatively influences the treatment compliance in the early group (r=-0,431, p=0,0002, LI vs r=-0,15, p=0,08, LII).

Analysing the above, we can conclude that the treatment of patients in the early phase of the disease due to the high activity during this period is aimed at the administration of increased doses of glucocorticosteroids, but also the administration of the basic therapy according to the T2T recommendations. However, the patient in the early period of the disease has a higher compliance to the treatment administered by the specialist. At the same time, we have shown that adherence to treatment during this period is more negatively influenced by the mental state and the level of studies of the patients.

4.4. Management of patients with early SLE

According to the tasks outlined, we described a pattern of conduct of patients with early SLE (Figure 10). Based on the data of the specialized literature regarding the specific and non-specific manifestations of the disease, the disease classification criteria from 1972, 1987, 1992 and 2012, but also the results of the present research we established the following management principles:

1. Patients presenting to the family physician with one or two specific manifestations of the increased frequency, such as pain in the small or large joints and/or specific skin manifestations:

photosensitivity and malar rash are taking into consideration. At the same time, less common symptoms such as oral / nasal ulcers and alopecia are considered. We recommend these patients to be thoroughly investigated for the presence of nonspecific manifestations of the disease, but with high frequency, which refers to fatigue, fever, myalgia or Raynaud's syndrome. At this stage, we suggest performing general blood tests, to highlight the inflammatory process (ESR, CRP) and to exclude haematological changes (anemia, leukopenia, lymphopenia, thrombocytopenia), the results will guide the clinical and paraclinical evaluation in the annual dynamics of the patient, for the next 5 years.

2. The presence of the association of one or two specific manifestations of the disease with non-specific manifestations, as well as the association of the haematological changes will require the consultation of the rheumatologist, with the indication of the ANA. The titre of these antibodies will imply the following behavioural tactic: titre<1:80, will suggest the absence of the diagnosis of SLE or probable SLE, which means that these patients must be at the annual record of the family doctor at least 5 years, by the annual evaluation of the ANA titre.

3. All patients with presence of three signs and symptoms, specific or nonspecific SLE, as well as haematological, and ANA>1:80, should be further investigated for the presence of other immunological criteria. The diagnosis is based on the presence of four SLICC classification criteria, 2012, but also the clinical rationale of the rheumatologist.

4. The management of the disease at the early stage after establishing the diagnosis is based on the evaluation of the disease activity and the prompt administration of the necessary treatment to approve the prognosis.

5. The multidimensional assessment of patients in the first years of illness is based on dynamics, quarterly, on disease activity, organ damage, assessment of comorbidities and quality of life of patients, with the determination of the factors that negatively influence these parameters and their eradication to approve the long-term disease prognosis.

6. At the same time, it is necessary to train patients and their relatives in order to self-assess the health status and to educate them in order to increase compliance to the treatment administered. It is recommended to form patient groups to create a relationship based on trust in order to identify the needs and strengthen the therapeutic education of patients with SLE.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

GENERAL CONCLUSIONS

1. The study showed that symptoms at the onset of systemic lupus erythematosus were distributed according to their frequency: joint pain with swelling (64,70%), followed by photosensitivity (58,82%), fatigue (42,64%), rash malar (32,35%) and fever (29,41%), thus defining the top early manifestations of the disease.

2. Following the analysis of the precursor manifestations of the disease we established 4 and 5 years before consulting the doctor, the patients had photosensitivity, arthralgia and subfertility, 2 and 3 years before supplemented with malar rash, weight loss and leukopenia. The year preceding the diagnosis was characterized by the completion of the clinical picture with fatigue, fever, thrombocytopenia and proteinuria.

3. According to the results of the research, the activity of SLE according to SLEDAI-2K and SLAM was high in group I, whereas the irreversible organ damage was noted insignificant in the same study group compared with patients with constituted disease. The analysis of the batches highlighted

the quality of life diminished by the physical (38,79 ± 10,60 and 36,76 ± 10,29 p., LI and LII) and mental (41,80 ± 10,83 and 41,97 ± 10,43 p., LI and LII) components with a more important decrease of the physical component in the constituted group.

4. As a result of the analysis of adherence to treatment, we found that in patients with early SLE the compliance is higher compared to the constituted group (p=0,02). The high educational status of patients as well as their depressed mental state negatively influences treatment adherence.

5. As a result of the present research, a personalized management scheme of patients with specific and non-specific manifestations of SLE was developed. Prompt treatment in the early period depending on the activity of the disease and the organic involvement is appropriate for approving the prognosis

PRACTICAL RECOMMENDATIONS

Is recommended:

1. Orientation and guidance of the patient's behaviour with the manifestations that can be attributed to SLE, at the level of the primary health care, for the early detection of the patients with the suspected disease and the referral to the specialized medical care, rheumatology, to establish the diagnosis and the correct management of the disease.
2. The guidance of patients with early SLE in accordance with the activity of the disease, the organ DI and comorbidities in order to indicate effective treatment in the early period of the disease and the prevention of long-term complications.
3. To focus on patient behaviour as an important factor in ensuring the quality of life of patients with early lupus and possible medical factors that diminish it, in order to improve their overall condition.
4. Optimizing the control of the disease by applying a prototype of the management of the patient with early SLE, elaborated within the study.

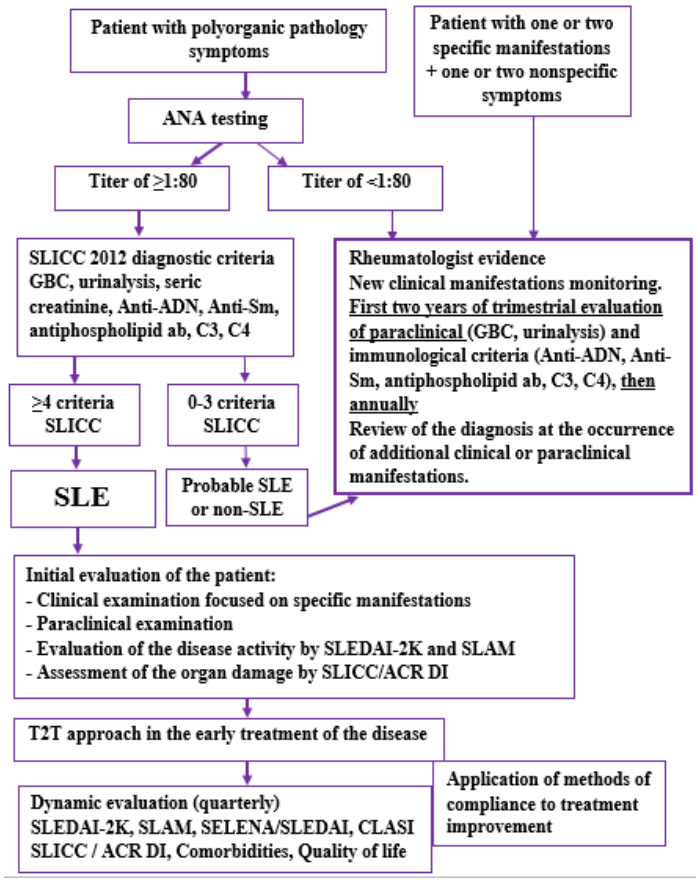

Figure 10. **Disease diagnosis and management behaviour in SLE patients.**

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- **Articles in scientific journals abroad:**

✓ **Articles in ISI, SCOPUS journals or other international databases.**

1. Mazur-Nicorici L., Sadovici-Bobeică V**.,** Loghin-Oprea N., **Garabajiu M.** et al. Disability in systemic lupus erythematosus. *Archives of the Balcan Medical Union*. 2018, vol 53, nr. 1, p. 35-40. ISSN 1584-9244.(**IF: 1.12**)
2. Mazur-Nicorici L., Sadovici-Bobeică V., **Garabajiu, M.,** Mazur, M. Therapeutic adeherence in patients with systemic lupus erythematosus: a cross-sectional study. *Rom J Internal Medicine.* 2018, vol. 56 (2), nr. 1, p. 109-115. ISSN: 2501-062X

- **Articles in accredited national scientific journals:**

✓ **articles in the category B journals**

3. Mazur-Nicorici L., **Garabajiu M.,** Sadovici-Bobeică V. et al. Evaluarea activității lupusului eritematos sistemic. *Sănătate Publică, Economie și Management în Medicină.* 2017, vol. 73, p. 149-150. ISSN 1729-8687.
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SCIENTIFIC-METHODICAL AND TEACHING WORKS

- **Clinical national protocol**

35. Mazur M., Mazur-Nicorici L., Vetrilă S., Sadovici- Bobeica V., Cebanu M., Șalaru V., **Garabajiu (Pașalî) M.** et al. Protocol clinic naţional „Lupus eritematos sistemic la adult". Aprobat prin ordinul Ministerului Sănătăţii, Muncii şi Protecţiei Sociale al Republicii Moldova nr. 381 din 07.03.2018

PARTICIPATIONS IN SCIENTIFIC FORUM

- **Participations with communications in scientific forums**

✓ **International**

1. Sadovici-Bobeică V., **Garabajiu M.,** Mazur-Nicorici L. et al. The association between hydroxychloroquin use and frequency and severity of SLE flares in MoLuStudy: results from a prospective, observational study. *35 Balkan Medical Week.* 25-27 septembrie 2018, Atena, Grecia.

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- **Participations with poster in scientific forums**

✓ **International**

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✓ **National**

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ABBREVIATION LIST

Anti dsDNA	Anti double stranded DNA antibodies
Anti CL	Anti Cardiolipin antibodies
Ac anti Sm	Anti Smith antibodies
Anti-β2GP1	Anti Beta2 Glycoprotein1 antibodies
ANA	Antinuclear Antibody
PUD	Peptic ulcer disease
CRD	Chronic renal disease
COPD	Chronic obstructive pulmonary disease
C3, C4	C3, C4 complement fractions
GCS	Glucocorticosteroids
HT	Hipertension
CCI	Charlson Comorbidity Index
MI	Miocardial infarction
MMAS-8	Morisky Medication Adherence Scale
CRP	C reactive protein
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
SLAM	Systemic Lupus Erythematosus Measure
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SLICC/ACR DI	Systemic Lupus International Collaborating Clinics Damage Index
VAS	Visual Analog Scale
GBC	General blood count
ESR	Erythrocyte sedimentation rate
CHF	Chronic heart failure